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(54) **Compositions and methods for use in targeting vascular destruction**

(57) Use of a prodrug that is substantially noncyto-  
toxic, but is convertible to a substantially cytotoxic drug  
by action of an endothelial enzyme selectively induced  
at enhanced levels at sites of vascular proliferation, other  
than combretastatin A4 disodium phosphate, in an

amount effective to achieve targeted vascular destruc-  
tion at a locality of proliferating vasculature, in the man-  
ufacture of a medicament for treating a warm-blooded  
animal having a vascular proliferative disorder.

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# EUROPEAN SEARCH REPORT

Application Number  
EP 07 00 8855

| DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                       |                                                  |                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------|
| Category                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Citation of document with indication, where appropriate, of relevant passages                                                                                                                                                                                                                                         | Relevant to claim                                | CLASSIFICATION OF THE APPLICATION (IPC)         |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | UEDA Y ET AL: "NOVEL WATER SOLUBLE PHOSPHATE PRODRUGS OF TAXOL POSSESSING IN VIVO ANTITUMOR ACTIVITY"<br>BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB,<br>vol. 3, no. 8, 1993, pages 1761-1766,<br>XP000570975<br>ISSN: 0960-894X                                                                             | 1-14                                             | INV.<br>A61K31/661<br>A61K31/6615<br>A61K31/664 |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | * abstract *                                                                                                                                                                                                                                                                                                          | 1-14                                             |                                                 |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | -----<br>DARK G G ET AL: "COMBRETASTATIN A-4 AN AGENT THAT DISPLAYS POTENT AND SELECTIVE TOXICITY TOWARD TUMOR VASCULATURE"<br>CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US,<br>vol. 57, no. 10, May 1997 (1997-05), pages 1829-1834, XP001008749<br>ISSN: 0008-5472<br>* page 1829 * | 1-14                                             |                                                 |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | -----<br>VYAS D M ET AL: "SYNTHESIS AND ANTITUMOR EVALUATION OF WATER SOLUBLE TAXOL PHOSPHATES"<br>BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB,<br>vol. 3, no. 6, 1993, pages 1357-1360,<br>XP000570956<br>ISSN: 0960-894X                                                                                   | 1-14                                             | TECHNICAL FIELDS SEARCHED (IPC)<br>A61K         |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | * abstract *                                                                                                                                                                                                                                                                                                          | 1-14                                             |                                                 |
| -----                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                       |                                                  |                                                 |
| <del>The present search report has been drawn up for all claims</del>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                       |                                                  |                                                 |
| Place of search<br>Berlin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                       | Date of completion of the search<br>13 June 2008 | Examiner<br>Beyss-Kahana, Ellen                 |
| <p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone<br/>Y : particularly relevant if combined with another document of the same category<br/>A : technological background<br/>O : non-written disclosure<br/>P : intermediate document</p> <p>T : theory or principle underlying the invention<br/>E : earlier patent document, but published on, or after the filing date<br/>D : document cited in the application<br/>L : document cited for other reasons<br/>.....<br/>&amp; : member of the same patent family, corresponding document</p> |                                                                                                                                                                                                                                                                                                                       |                                                  |                                                 |

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EPO FORM 1503 03/92 (P04C01)



European Patent  
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Application Number

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### CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1-14 partially

☐ The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-14 partially

Use of a phosphate prodrug of Combretastatin A-1 according to formula 3-8 for the preparation of a medicament for the treatment of a vascular proliferative disorder

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2. claims: 1-14 partially

Use of a phosphate prodrug of Dihydronaphthalene according to formula 11, 12 for the preparation of a medicament for the treatment of a vascular proliferative disorder

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3. claims: 1-14 partially

Use of a phosphate prodrug of Pancratistatin according to formula 13, 14 for the preparation of a medicament for the treatment of a vascular proliferative disorder

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4. claims: 1-14 partially

Use of a phosphate prodrug of the Benzothiophene according to formula 15, 16 for the preparation of a medicament for the treatment of a vascular proliferative disorder

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5. claims: 1-14 partially

Use of a phosphate prodrug of the Indole according to formula 17, 18 for the preparation of a medicament for the treatment of a vascular proliferative disorder

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6. claims: 1-14 partially

Use of a phosphate prodrug of Colchicine according to formula 19, 20 for the preparation of a medicament for the treatment of a vascular proliferative disorder

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7. claims: 1-14 partially

Use of a phosphate prodrug of Methoxyestradiol according to formula 21, 22 for the preparation of a medicament for the treatment of a vascular proliferative disorder

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